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# AN OUTBREAK OF TOXIC JAUNDICE DUE TO TETRACHLORETHANE POISONING

A NEW TYPE AMONGST AEROPLANE WORKERS


BY

WILLIAM HENRY WILLCOX, M.D., B.Sc. LOND.,

F.R.C.P. LOND., F.I.C., D.P.H., &c.,

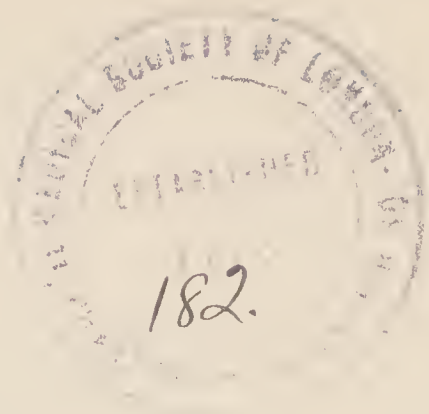
PHYSICIAN TO ST. MARY'S HOSPITAL; SENIOR SCIENTIFIC ANALYST  
TO THE HOME OFFICE, ENGLAND.

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AN OUTBREAK OF  
TOXIC JAUNDICE DUE TO TETRACHLOR-  
ETHANE POISONING.

A NEW TYPE AMONGST AEROPLANE WORKERS.<sup>1</sup>

IN September and October of 1914 the occurrence of several cases of illness associated with jaundice was noticed at the Hendon Aeroplane Factory. Cases of a similar nature were later observed at other aeroplane and seaplane factories. The outbreak of war naturally caused greatly increased activity in these factories, and the workers were employed overtime, so that any toxic influences to which they might be exposed in their work would be greatly increased.

My first acquaintance with the subject of my paper was on Nov. 5th, 1914, at my out-patient department at St. Mary's Hospital. The case was as follows.

CASE 1.—The patient was a man aged 36. The history of his case was that he had been employed at the Hendon Aeroplane Factory since August 8th. On Oct. 24th patient felt ill; he had nausea and retching in the morning, some slight pain in upper abdomen, and jaundice. He gave up work. His symptoms increased in severity. At my examination there was marked jaundice present; the patient appeared seriously ill. Pulse 96; temperature 99·5° F. Liver felt about 1 inch below right subcostal border in right nipple line on inspiration. No abdominal tenderness was present; no anæmia. Patient said the stools were pale and urine high-coloured. There was no history or evidence of syphilis or alcoholism. The tongue was furred and dry. Patient said he thought his illness was

<sup>1</sup> A paper read before the Medical Society of London on March 1st, 1915.

due to some condition associated with his work because ten other workers were affected similarly. On inquiry he stated that aeroplane "dope" was used in the factory, and he thought this was composed of "collodion, chloroform, ether, and acetone." He said that men who did not use the dope also suffered from the illness, but several of those who were using the dope had been taken ill. A diagnosis of toxic jaundice was made, and it was thought probable that some constituent of the dope was the cause of patient's illness. I did not see the patient again, but I heard that on Nov. 14th he was admitted to the Middlesex Hospital and died there on the 26th.

The case was referred to Mr. Luxmore Drew, H.M. coroner, and he after careful consideration decided that a post-mortem examination should be held. This was made by Dr. Spilsbury, who found a shrunken liver markedly bile-stained. Dr. T. M. Legge, Medical Inspector of Factories, Home Office, also investigated the case, and it was thought that the condition of the liver might be connected with the action of some poison to which the deceased was exposed during life.

A number of animal experiments were conducted by me relating to the possible toxic action of the constituents of the dopes used at the aeroplane factory, and it was clearly demonstrated that one of the constituents—viz., tetrachlorethane—was a powerful liver and kidney poison, causing fatty degeneration of the cells of these organs.

Careful investigations were made by Dr. Legge and myself into the health of other employees at the factory and into the conditions of work there.

All the facts were carefully placed before the learned coroner, Mr. Luxmore Drew, who made a most careful and painstaking inquiry into the case, and as a result the jury found that death was due to degeneration of the liver caused by tetrachlorethane present in the cellulose varnish or dope used by deceased and to the vapours of which he was exposed during life.

A number of other cases have been carefully examined by me, thus :—

CASE 2.—Male aged 48. Began work on August 10th, 1914 ; left work on Oct. 19th. He complained of constipation, sick headache, jaundice, nausea, and weakness, and some soreness of eyes. The urine was high-coloured ; stools were pale. Patient returned to work on Nov. 9th, but gave up work again on the 23rd. On examination on Dec. 10th definite enlargement of liver was noticed ; it was not tender. Slight jaundice was present but definite. Patient made a good recovery on being kept away from his work.



CASE 3.—Male aged 23. He commenced work on August 26th, 1914; gave up work on Nov. 30th. He complained of nausea, sickness in morning, and some slight pain in upper abdomen. He had been working near where doping was done. On examination on Dec. 3rd slight icterus was present; no anæmia; the liver was slightly enlarged; pulse 96. Patient made a good recovery on being kept away from his work.

CASE 4.—Male aged 53. He commenced work on August 31st, 1914; gave up work on Oct. 27th. He was weak and ill, with loss of appetite. He had dryness of throat. He was sick daily for 14 days. He was light-headed at night. He had definite jaundice, the urine being high-coloured and the stools pale. There was no abdominal pain. The liver was slightly enlarged. Slight but definite icterus was present; no anæmia. Patient made a good recovery.

CASE 5.—Male aged 44. He commenced work on August 22nd, 1914; gave up work on Nov. 30th. He complained of irritation of throat, loss of appetite, drowsiness, headache, and vomiting on two occasions before giving up work. Slight but definite jaundice was present on Dec. 10th. The liver was slightly enlarged; no tenderness over it. Patient made a good recovery.

CASE 6.—Male aged 47. He began work on Sept. 22nd, 1914; gave up work on Nov. 23rd. He did much overtime and used dope. He had loss of appetite, nausea, constipation, drowsiness, sickness in morning, and definite jaundice. The stools were pale and urine high-coloured. On examination the liver was found slightly enlarged. Patient said he was a bilious subject. He made a good recovery.

CASE 7.—Male aged 28. He began work on August 13th, 1914; gave up work on Nov. 7th. He returned to work on Nov. 14th and gave up work again on the 21st. Patient had loss of appetite, nausea, vomiting at times, constipation, drowsiness at work, and dryness in throat. On examination definite jaundice was present. There was no abdominal tenderness. Slight enlargement of liver was present. Patient made a good recovery.

CASE 8.—Male aged 24. He commenced work on August 14th, 1914. He used the dope varnish. He very soon began to feel ill. He suffered from loss of appetite, nausea, constipation, headaches, and nasty taste in back of throat; was drowsy while at work; general weakness was complained of. He gave up work on Dec. 7th. On examination there was slight but definite jaundice. Temperature

99·2°F. The liver was somewhat enlarged, the lower border reaching three-quarters of an inch below right subcostal border in the right nipple line. There was no tenderness in abdomen. No signs of alcoholism or syphilis were present. He said the stools had been biscuit coloured. The patient made a good recovery.

CASE 9.—Male aged 49. He commenced work on Sept. 15th, 1914; at once began to feel ill. He suffered from drowsiness, constipation, and slight headache. The stools became pale in colour. There was no abdominal pain. Definite jaundice occurred on Oct. 7th, but cleared up before Nov. 2nd. He gave up work, but resumed again on Nov. 2nd; the symptoms at once recurred. He now had sickness and the jaundice reappeared on Nov. 19th. He gave up work for the second time. The jaundice was now deeper than before, the stools were pale, and urine dark coloured. On examination on Dec. 17th there was still definite jaundice of slight depth. The liver was slightly enlarged, the lower border reaching half an inch below right subcostal border on inspiration. Patient improved slowly, but got well.

CASE 10.—Male aged 31. He commenced work on August 12th, 1914. He began to feel ill about Dec. 1st. He complained of loss of appetite, headache, peculiar taste in mouth, drowsiness, nausea, and retching in morning. He was sick on Jan. 6th, 8th, and 9th, 1915. He became slightly jaundiced and gave up work on Jan. 9th. On examination on the 11th slight icterus was present. The liver was slightly enlarged, being felt about half an inch below subcostal border in right nipple line. Patient seemed in a marked toxic condition considering the slight amount of icterus present. He made a good recovery.

CASE 11.—Male aged 58. He began to work at Hendon on June 3rd, 1914. He was working close to where the dope was used. He left work on Sept. 21st. He was weak, felt drowsy, had no appetite, no energy, and the bowels were constipated. He had nausea, vomiting on one occasion. Jaundice developed on Sept. 14th. The patient became deeply jaundiced, with pale stools and high-coloured urine. He went to hospital on Oct. 2nd and was in there seven weeks. He developed ascites while in hospital and this increased. Oedema of the legs also developed. The urine on examination by Dr. J. M. Bernstein showed a deposit of leucin. On Jan. 1st, 1915, paracentesis was performed by me and 22 pints of clear ascitic fluid were drawn off. The fluid gradually reaccumulated, and about three weeks later paracentesis was again performed by Dr. W. H. Ogle-Skan, who removed 21 pints of ascitic fluid. The fluid reaccumulated after this tapping, but Dr. Ogle-Skan tells me that absorp-

tion of the fluid has commenced and that patient is much improved in health and strength, and seems in a fair way to recovery. There was no history or evidence of alcoholism or syphilis in this case.

Other cases than those above described occurred at Hendon, but these are all on which a detailed clinical examination was made by me. In none of the above cases was there a history of alcoholic excess or of syphilis. In several of the cases the Wassermann test for syphilis was applied, but in every case the result was negative.

On Dec. 4th, 1914, I visited the Hendon aeroplane works. The smell of tetrachlorethane was very much in evidence, and at that time the ventilating arrangements by the plenum system were such that the heavy vapour of the dope was blown about the large room of the factory instead of being extracted. A reference to a plan on which were marked the places where affected persons worked showed that several cases of jaundice occurred at quite considerable distances—e.g., 30 or 40 yards—from where the dope varnishing was done. The more severe cases occurred in persons who were actually using the dope or were near where it was used. On questioning some of those working in the factory at the time of my visit I found that several workers complained of nausea, biliousness, drowsiness, constipation, loss of appetite, nasty taste at the back of the throat, headache, and general malaise, these symptoms being no doubt due to the dope vapour.

Cases of illness similar to those at Hendon have occurred in other factories where tetrachlorethane has been used. At the aeroplane factory at Crayford two severe cases occurred.

CASE 12.—Female aged 19. She commenced work in August, 1914. About Nov. 15th the patient complained of the smell of the dope, of discomfort in throat, and drowsiness. On Dec. 27th she became acutely ill with jaundice; there was vomiting and some abdominal pain. She became worse and on Jan. 2nd, 1915, vomited blood, was stuporose, and had convulsive twitchings. The stupor deepened into coma which lasted two days, when death supervened.

*Necropsy.*—The liver was hard and firm; it was very



yellow and showed marked congestion; weight  $34\frac{1}{2}$  oz. The kidneys showed marked yellow staining of the cortex, the pyramids being intensely congested. The medulla was yellow and congested. The kidneys weighed each 5 oz. The heart weighed  $7\frac{1}{2}$  oz. The muscle showed yellow staining; some pink staining of endocardium. Numerous petechiæ were present over surface of left ventricle. The small intestine showed intense petechial hæmorrhage over the surface. There was marked congestion of the small intestine. The spleen weighed 8 oz.; it was hard and firm. Microscopical examination of the liver showed extensive necrosis, and in the kidney fatty degeneration was present.

CASE 13.—Female aged 17. She was working in the aeroplane factory for 4 months. On Jan. 14th, 1915, she felt ill; complained of discomfort in throat and general weakness. On the 28th she gave up work. She complained of nausea, sickness, and constipation. Jaundice occurred at this date. Patient was examined on Feb. 25th. There were intense jaundice, stupor, and delirium. The liver could not be felt. Spleen could not be felt. There was some dulness in flanks, which became resonant when patient rolled on to side. The urine contained much bile and a trace of albumin; many epithelial and granular casts were present. Patient became worse, passing into coma, and death occurred on Feb. 28th.

A fatal case occurred at the Seaplane Works, Rochester.

CASE 14.—Female aged 34. She commenced work in September, 1914. She worked overtime. On Dec. 7th she complained of feeling of illness and loss of appetite. On the 21st she gave up work. She was then jaundiced and complained of biliousness; she had abdominal discomfort, vomiting, and headache; constipation was present. On the 23rd she was dazed and confused; could not understand questions. On the 24th there was more severe abdominal pain and very deep jaundice. On the 25th she became drowsy, very little urine being passed. Delirium occurred on the 27th, and patient passed into coma, death occurring on Jan. 1st, 1915.

*Necropsy.*—The liver was shrunken; weight 20 oz. It was hard and firm. There was intense yellow staining. Gall-bladder was normal. The small intestine and mesentery showed marked congestion. The kidneys showed yellow staining of cortex and intense congestion of pyramids. Microscopical examination showed necrosis and degeneration of the liver cells, and fatty degeneration of the cells of the kidney.



### *Symptoms.*

The following is a general résumé of the symptoms of tetrachlorethane poisoning. For some days the patients complain of general malaise, drowsiness while at work, loss of appetite, nausea, retching in the morning, unpleasant taste in the throat, constipation usually, and headache. Abdominal discomfort is present in some cases. After indefinite symptoms of this kind, lasting several days or even weeks, definite jaundice develops, and this is associated with pale stools and bilious urine. Vomiting is now likely to become more marked. The patient may become mentally confused, stuporose, or delirious. In acute cases hæmatemesis or convulsions may occur. Coma supervenes and death results. In the toxic stage of the disease purpuric rash and hæmorrhages may occur. Suppression of urine also occurs towards the end.

If the patient is removed from the influence of the poison in the early stages of the illness the symptoms clear up, but it is some weeks before the jaundice becomes completely free, even if it is only slightly marked. In cases with deep jaundice the prognosis is bad and recovery is unlikely. In one very interesting case (No. 11, Hendon Series) the patient recovered from the acute symptoms of a rather severe attack, but afterwards signs of contraction of the liver with portal obstruction developed, marked ascites resulting. It is interesting to record that after two operations of paracentesis the patient is making a good recovery.

In the early stages of the illness the liver appears to be slightly enlarged, no abdominal tenderness being present. Later the liver diminishes in size. The urine contains in the late stages of a severe course much bile, a small amount of albumin and numerous casts, epithelial and granular casts predominating. No leucin and tyrosin crystals have been found by me in the unconcentrated urine, but as I have only had an opportunity of examining the urine in one acute case shortly before death I cannot speak as to the frequency of occurrence of

leucin and tyrosin crystals. No acetone or diacetic acid has been found in the urines examined.

Interesting clinical features of the action of tetrachlorethane on the liver in the case of the aeroplane workers in this country are: (1) The insidious onset of the symptoms. (2) The comparatively long duration of the acute stage when marked jaundice has supervened, thus distinguishing the cases from acute yellow atrophy of the liver. (3) The absence of marked pyrexia, thus distinguishing the cases from infectious jaundice (Weil's disease). (4) The absence of anæmia, thus distinguishing the cases from poisoning by poisons which cause marked blood destruction—e.g., arseniuretted hydrogen, &c. (5) The marked depth of the jaundice, which is much deeper than is usually seen in cases of delayed chloroform poisoning.

There seems to be a marked variation in the susceptibility of certain persons to the poison, and this corresponds to the varying susceptibility of patients to other liver poisons—e.g., chloroform as described by Dr. L. G. Guthrie.

The jaundice appears to be of the toxæmic type, or hæmohepatogenous jaundice of Rolleston, and the exact type of the symptoms appears to be distinguishable from those of previously described liver poisons. There is no doubt that the question of dosage plays a very important part in the type of symptoms and in the incidence-rate of the illness. Thus the body is able to deal with very small amounts of the poison. When the quantity of poison absorbed becomes greater than the amount which can be dealt with, then symptoms result, and these will be progressive unless the patient is removed from the influence of the poison. The effect of increased dosage in causing illness is well shown by the effects of overtime and the increase in the quantity of dope varnish used in causing illness, whereas under previous conditions no harm resulted to the health of the workers.

It is interesting to record that on May 13th, 1914, a report was issued by Dr. Heffter and Dr. Kraus on Industrial Poisoning by Tetrachlorethane. In Germany the dope used contained a much higher percentage of tetrachlorethane than the English

varnishes. As a result of this two types of symptoms resulted: (1) In one type of case gastrointestinal and hepatic occurred as in the English cases; (2) in the other type of case nervous symptoms predominated, the patients suffering from tremors, headache, pains in limbs, numbness, pins and needles of extremities, loss of knee-jerks, and excessive sweating. In the German investigations some experiments on animals were carried out with a view to showing the anæsthetic action of the drug, but no post-mortem examination was made on the animals treated, and no direct proof was afforded of the poisonous action of tetrachlorethane on the liver.

### *Treatment.*

Prevention of poisoning by the vapour of tetrachlorethane is of much greater importance than the treatment of patients suffering from this intoxication. Effective measures have been instituted in all factories where tetrachlorethane is used whereby the heavy vapour is removed by powerful extraction fans, which remove the vapour at a low level and rapidly withdraw it from the workers. The Home Office have taken prompt action in the issuing of warning instructions, and in ensuring the provision of satisfactory measures for removal as far as possible of any danger to workers from the vapour of the dope used.

The treatment of patients suffering from toxic jaundice due to "dope vapour" consists firstly in their removal from all influence of the poison. Rest, light diet containing a much reduced amount of proteid, saline aperients, and general hygienic measures are all that are necessary in mild cases. It is important that a patient should not be allowed to return to his work for a long period, at least a month elapsing after the jaundice has quite cleared up. Resumption of work should not be permitted unless the methods of removal of tetrachlorethane vapour in the factory where the patient is employed are effective.



*Toxicological Aspects.*

In considering the Hendon cases the first question that arose was, Were the symptoms due to some natural disease such as catarrhal jaundice, acute yellow atrophy, or jaundice of an infectious type; or were they due to some poison which had a special action on the liver? A careful review of the cases indicated that the symptoms were not consistent with natural disease, but were indicative of some poison acting on the liver.

The conditions obtaining at the aeroplane factories rendered it extremely probable that the "dope" vapour which contaminated the air to which the workers were exposed was responsible for the outbreak of illness. Also the conditions of work showed on investigating the individual cases that those workers who had been most exposed to dope vapour were most likely to suffer from illness, and speaking broadly the severity of the illness corresponded to the extent to which the patient had been exposed to dope vapour.

*Dope or Cellulose Varnish.*

This is a solution of acetate of cellulose in a mixture of benzene, acetone, methylated spirit, and tetrachlorethane. The proportions of the constituents vary with different types of varnish. The dope is a viscid, colourless liquid smelling something like chloroform. If applied to calico it forms on drying a firm, airtight and waterproof coating. Several coats of dope are given to the calico stretched on the framework of the aeroplane wings. The evaporation of the dope does not lead to a separation of its volatile constituents. A vapour comes off which appears to be a mixture of the volatile constituents of the dope. The vapour density of this was found to be 1.91 times that of air. If dope is distilled the bulk of the liquid distils over from 63° to 80° C., although the boiling point of tetrachlorethane is 147° C.

It is necessary for the drying to take place in a warm chamber. It appears that tetrachlorethane

is a valuable constituent of the dope, since there is difficulty in getting such a good firm coating with a cellulose varnish in which tetrachlorethane is not present.

Experiments were instituted to test each of the constituents of the dope and the dope itself as regards the toxic action of their vapour on the liver.

For each experiment a large glass chamber (dessicator) was used. In the bottom of this were placed daily 10 c.c. of the liquid to be tested. A perforated zinc platform was stretched across the middle of the chamber—i.e., half way up. On this were placed the animals to be experimented upon. The top of the chamber was covered with a perforated zinc roof. Rats were selected as the most suitable animals. The animals were kept in the glass chamber for eight hours a day for a week.

The liquids tested were dope, tetrachlorethane, acetone, benzene, and methylated spirit respectively. Two rats were placed in each chamber, five experiments being carried out together.

The rats thus exposed to dope vapour and tetrachlorethane vapour became very drowsy and slept all day. After removal from the chamber they remained drowsy for some little time, and on some occasions they were quite ataxic in gait, falling over on to their sides. After an hour or more usually they fed and became active. These animals did not gain in weight during the week's treatment.

In the experiments with acetone, benzene, and methylated spirit the animals were drowsy while exposed to the respective vapours, but on removal from it they immediately became lively and fed well. No ataxic symptoms were observed. All these animals gained markedly in weight during the week.

After seven days' treatment the animals were killed, and post-mortem examinations were made on them by Dr. Spilsbury and myself. The tetrachlorethane rats showed marked changes in the liver to the naked eye, there being fatty degeneration and bile-staining present. The "dope" rats showed similar changes but less marked. The rats exposed to the vapour of benzene, acetone, and methylated spirit showed no changes in the liver to the naked eye.

Careful microscopical examination of the organs showed marked fatty degeneration and cloudy swelling in the liver and kidneys of rats exposed to dope vapour and tetrachlorethane vapour, but no abnormal change in the animals exposed to the other vapours. Rats were also exposed to the action of dope vapour and tetrachlorethane vapour for five weeks. Marked diminution in size in the liver occurred in

each case. The liver and kidneys were pale on section. They showed cloudy swelling and fatty degeneration.

The above experiments showed conclusively that tetrachlorethane is a powerful liver poison, and also they show that dope vapour is a liver poison, and that the poisonous property of dope vapour is due to tetrachlorethane being present in it.

In 1909 I made several experiments with tetrachlorethane on cats and rats in order to determine the anæsthetic effect of the drug. The vapour was found to be a powerful anæsthetic, but after removal from the vapour it was a long time before the animal recovered from the effects, sometimes 24 hours or more being required. It was obvious that tetrachlorethane was much more poisonous than chloroform as regards its anæsthetic effects.

About this time experiments were carried out by Dr. Veley, F.R.S., in the Physiological Laboratory of the University of London, and these showed that, weight for weight, tetrachlorethane was 2·8 times as powerful a tissue poison as chloroform.<sup>2</sup>

CHCl<sub>2</sub>.  
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CHCl<sub>2</sub>.

Tetrachlorethane is a colourless liquid,

Its boiling point is 147° and specific gravity 1·614. It has a smell like that of chloroform. It is not inflammable. It is known as acetylene tetrachloride and by the trade name of "cellon." It is used largely owing to its excellent solvent properties for resins, acetate of cellulose, &c.

There is no doubt that this compound is a powerful poison to the liver and kidneys, and that it is also a powerful narcotic poison. Every care should be taken in the use of tetrachlorethane to prevent as far as possible inhalation of the vapour.

Welbeck-street, W.

<sup>2</sup> Proceedings of the Royal Society, Series B, vol. lxxxii., 1910.





